UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WISCONSIN

PROMEGA CORPORATION,

Plaintiff,

and

MAX-PLANCK-GESELLSCHAFT zur FORDERUNG der WISSENSCHAFTEN E.V.,

Involuntary Plaintiff,

v.

LIFE TECHNOLOGIES CORPORATION, INVITROGEN IP HOLDINGS, INC., and APPLIED BIOSYSTEMS, LLC,

Defendants.

Case No. 10-cv-281-bbc

PROPOSED FINDINGS OF FACT IN SUPPORT OF DEFENDANTS' MOTION FOR PARTIAL SUMMARY JUDGMENT OF NONINFRINGEMENT OF THE PROMEGA PATENTS AND ALTERNATIVELY INVALIDITY

Defendants submit the following Proposed Findings of Fact in support of their Motion for Summary Judgment of Invalidity and Alternatively Noninfringement. All evidence cited herein is appended to the Declaration of Amy Sun in Support of Defendants' Motion for Summary Judgment of Invalidity and Alternatively Noninfringement ("Sun Decl."), filed concurrently herewith.

DEFENDANTS' PROPOSED FINDINGS OF FACT

1. The accused AmpFlSTR® kits provide components for carrying out the simultaneous amplification (copying) of multiple short tandem repeat (STR) loci from one or more DNA samples. Sun Decl., Ex. 1.

2. DNA is a double-stranded molecule consisting essentially of two complementary strands of nucleotides. Sun Decl., Ex. 9 (Struhl Noninfringement Report) ¶ 3; Ex. 10 (Booker Noninfringement Report) ¶ 3.

3. The four nucleotides which are found in DNA are adenine (A), thymine (T), guanine (G), and cytosine (C). Id.

4. An STR locus is a region of DNA which contains repeats of a particular nucleotide sequence. Id. For example, the DNA sequence ATT (adenine-thymine-thymine) may be repeated ten times in tandem (*i.e.* in a row) at a particular locus. Id.

5. The number of repeats of a given sequence at a particular STR locus varies highly from individual to individual. Sun Decl., Ex. 9 (Struhl Noninfringement Report) ¶ 4; Ex. 10 (Booker Noninfringement Report) ¶ 4.

6. Such length and/or sequence variation is referred to as "polymorphism." Id.

7. A region, or locus, of DNA in which such variation occurs is referred to as a "polymorphic locus." Id. For example, one individual's DNA may have eleven CCCG (cytosine-cytosine-cytosine-guanine) repeats at a given STR locus, while another individual may have fourteen at the same locus. Id.

8. Each of these variations is referred to as an "allele" (or "marker") of the particular locus. Id.

9. Each individual has two alleles for every STR locus, one inherited maternally and the other paternally. Id.

10. Determining the unique set of alleles at multiple loci in an individual's DNA gives rise to an STR profile or fingerprint unique to the individual. Sun Decl., Ex. 9 (Struhl Noninfringement Report) ¶ 5; Ex. 10 (Booker Noninfringement Report) ¶ 5.

11. This method is known as STR profiling and can serve as the basis for identifying individuals, determining whether two samples are a match or originate from two individuals, determining whether one sample contains a mixture of two individuals' DNA, etc. Id.

12. STR profiling is useful in many fields, including forensic science, paternity testing, bone marrow transplant monitoring, cell line authentication, linkage mapping, etc. Id.

13. When performing STR analysis, it is necessary to amplify (make copies of) the STR loci of interest in order to obtain a detectable amount for analysis. Sun Decl., Ex. 9 (Struhl Noninfringement Report) ¶ 6; Ex. 10 (Booker Noninfringement Report) ¶ 6.

14. For reasons of efficiency, it is advantageous to co-amplify, or multiplex, several loci in a single reaction rather than individually. Id.

15. Amplification of STR loci is most commonly carried out by the polymerase chain reaction (PCR). Id.

16. The basic idea of PCR is to (1) separate double-stranded DNA into single strands, (2) allow primers which specifically target the desired STR loci to bind to the single strands at the target loci, (3) replicate the single strands beginning at these primer sites into double-stranded DNA again, and (4) repeat the process until a sufficient amount of copies of the desired STR loci is generated. Id.

17. In multiplex PCR amplification reactions, multiple STR loci are simultaneously targeted and multiple corresponding primers are used simultaneously in a single reaction. Id.

18. The Promega patents relate to multiplex amplification of certain sets of STR loci. *See generally* Sun Decl., Ex. 2; Ex. 3; Ex. 4; Ex. 5. *See also* Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 4.

19. A person of ordinary skill in the art of the Promega patents would be one having a bachelor's degree in biology, biochemistry, molecular biology, or related fields, or the equivalent. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 2; Ex. 23 (Ballantyne Validity Report) ¶ 2; Ex. 24 (Dimond Validity Report) ¶ 2. Additionally, he would have several years of experience working in a laboratory and be familiar with basic DNA manipulation techniques, primer design, PCR, and multiplex PCR. Id. He would also be familiar with DNA detection techniques such as gel electrophoresis, capillary electrophoresis, fluorescent dye labeling, and genetic testing. Id.

20. The concept of multiplex amplification reactions is not new to the Promega patents. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶¶ 5, 12; Ex. 15; Ex. 16.

21. The concept of multiplex amplification reactions first emerged in the late 1980s. Id.

22. The concept of multiplexing STR loci is not new to the Promega patents. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 12; Ex. 17 (Kimpton '94); Ex. 18 (Kimpton '93); Ex. 19 (Caskey); Ex. 20 (Edwards).

23. A number of publications demonstrate that by the early 1990s, scientists were attempting and successfully carrying out multiplex reactions of new and different sets of STR

loci. Sun Decl., Ex. 17 (Kimpton '94); Ex. 18 (Kimpton '93); Ex. 19 (Caskey); Ex. 20 (Edwards).

24. Despite its widespread adoption, multiplex PCR remained an unpredictable and experimental method. Sun Decl., Ex. 8 (Struhl Invalidity Report), ¶ 7.

25. Scientists discovered unexpectedly that co-amplifying multiple loci together was more complicated than simply consolidating multiple individual amplification reactions into one. Id.

26. Multiplexing could produce artifacts and introduce issues which did not arise when performing single locus amplification. Id.

27. Although scientists were discovering ways to multiplex specific sets of loci, there was no standard protocol which enabled certain, consistent, and clean co-amplification of any arbitrary set of loci. Id. ¶ 8.

28. Skilled artisans had not yet managed to discover a universal method or standard protocol for multiplexing STR loci which eliminated the trial and error experimentation necessary to eliminate or minimize problems such as locus to locus imbalance, artifact bands, etc. Id. ¶¶ 8, 42.

29. Scientists could not predict with any certainty, absent a preexisting publication or teaching, whether a given set of loci would co-amplify successfully together. Id. ¶ 8.

30. Each new set of loci had to be tested and optimized through trial and error experimentation. Id. ¶ 9.

31. This was true even when adding a new locus to an already successful multiplex, as it could not be predicted how the loci would interact with each other or how effectively and efficiently the primers would work in a single reaction environment. Id.

32. Creating a successful multiplex became more complicated with the addition of each new locus, *i.e.*, adding an eighth locus to a 7-plex was more complicated than adding a seventh locus to a 6-plex. Id.; Sun Decl., Ex. 25 (Gibbs Report) at 18, 23.

33. It was necessary to determine whether the loci would co-amplify together; develop primer pairs that would co-amplify together and not interfere with each other; avoid undesirable results such as nonspecific amplification or primer-dimer formation; and adjust a number of reaction parameters such as temperature, the number of amplification cycles, and the concentration of primers, enzyme, buffer, dNTP, etc. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 9.

34. Primers were the crucial component of any multiplex reaction. Id. ¶ 10.

35. If successful co-amplification could not be achieved by adjusting the above parameters, new primer candidates would have to be designed and tested. Id.

36. The identification of primer pairs for each locus that worked together in a multiplex and produced clean results would often take several tries (and sometimes many tries) and significant time. Id.

37. While general rules and guidelines existed, they did not guarantee that a given set of loci would co-amplify or that, even if it did, the multiplex would be free of artifacts or other issues. Id. ¶ 11.

38. Allele overlap occurs when alleles of different STR loci are similar in size and thus overlap each other when they are visualized, rendering assignment of alleles to a specific locus difficult or impossible. Id. ¶ 14.

39. Several of the loci listed in the claims of the Promega patents were known and had been multiplexed in the prior art. Sun Decl., Ex. 2 ('660 patent), col. 3, ll. 46-47; Sun Decl., Ex. 3 ('598 patent), col. 2, ll. 37-38.

40. All of the loci listed in the claims of the '598 patent were known and had been multiplexed in the prior art. Sun Decl., Ex. 13 at 239.

41. Several of the primers used to multiplex the loci listed in the claims of the Promega patents were known and had been used in multiplex reactions of STR loci in the prior art. *E.g.*, Sun Decl., Ex. 13 at 105.

42. By the early 1990s, fluorescence-based detection of PCR amplification products had also begun to supersede older detection technologies such as radioactivity, gel electrophoresis, and autoradioagraphy, allowing for rapid, safe, and sensitive evaluation of PCR products. Sun Decl., Ex. 8 (Struhl Invalidity Report), ¶ 6.

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By: /s/ Amy Sun

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